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Original Article

The influence of breathing mode on tobramycin serum levels using the I-neb AAD system in adults with cystic fibrosis

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Abstract

Background: The clinical effectiveness of inhaled tobramycin depends on the dose reaching the desired regions of the lungs. This study evaluates the influence of breathing mode on tobramycin lung deposition using its pharmacokinetics as surrogate for deposition.
Methods: In a randomized, open-label, crossover study lung deposition in 18 adult CF patients is evaluated following inhalation of tobramycin aerosol using the I-neb nebulizer with TBM (Tidal Breathing Mode) and TIM (Target Inhalation Mode) breathing patterns. Breathing in TIM forced the patient to inhale in a slow and deep manner. Patients were categorized in three subgroups according to their lung function: ≤59%, 60–79% or ≥80% of FEV1 predicted. Blood samples were collected in order to model tobramycin pharmacokinetics. Nebulization time was recorded.
Results: Inhalation with TIM resulted in significantly higher maximum serum levels and area under the concentration–time curves (0–24 h). Mean bioavailability of TIM relative to TBM was 1.53 ± 0.41. Mean nebulization time was reduced by half with TIM. Subgroup category did not affect the results.
Conclusions: Slow and deep inhalation of aerosolized tobramycin resulted in higher lung deposition and shorter nebulization time compared to tidal breathing, regardless of the disease severity of the CF patient.
Dutch trial register number NTR3109.

Keywords: Aerosol; Tobramycin; Lung deposition; Breathing mode; Inhalation; Pharmacokinetics

1. Introduction

Pulmonary complications are responsible for the majority of morbidity and virtually all mortality in cystic fibrosis (CF) [1]. Due to increased mucus viscosity in the respiratory tract mucociliary clearance is impaired and the lungs become colonized and infected with bacteria, of which *Pseudomonas aeruginosa* (*Pa*) is the most important pathogen in CF lung disease [2]. Tobramycin inhalation is one of the antibiotics recommended in the treatment of chronic *Pa* infection in patients with CF [3].

The clinical effectiveness of inhaled antibiotics depends on the dose reaching the desired regions of the lungs. *Pa* is present in both the large and small airways. Yet a high peripheral deposition seems desirable because of the exponentially increasing surface area from the central lung towards the alveoli [4]. Inhalation of aerosols with a mass median aerodynamic diameter of 2–3 μm in combination with a slow deep breathing pattern has been found to result in optimal peripheral deposition [5]. However, tobramycin is licensed to be administered with a less efficient jet nebulizer

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leading to preferential central drug deposition due to tidal breathing and highly variable particle size distributions. More efficient and breath-controlled nebulizers have been developed in recent years, such as the I-neb nebulizer [6]. The I-neb can deliver homogenously-sized aerosols within the respirable range with two different breathing patterns: Tidal Breathing Mode (TBM) and Target Inhalation Mode (TIM). A recent crossover imaging study of 12 healthy subjects inhaling radiolabeled saline showed that lung deposition was significantly higher and nebulization time was shorter for TIM compared to TBM [7]. To our knowledge no randomized deposition studies with the I-neb have been carried out in CF patients.

It is possible that the benefits of current inhaled antibiotics in CF could be enhanced by targeting the peripheral airways using a slow and deep breathing mode during inhalation. The aim of this study was to compare deposition of aerosolized tobramycin delivered with the I-neb nebulizer between TIM and TBM breathing patterns in CF patients with different disease severity, using tobramycin pharmacokinetics as surrogate for lung deposition. Disease severity of the individual patient may be an important determinant, since inter-patient variability in lung deposition is known to be large in CF patients [8].

2. Methods

2.1. Study population

The study was performed in the Centre for Cystic Fibrosis, Haga Teaching Hospital, The Hague, The Netherlands. Patients aged 18 years or older and with a confirmed diagnosis of CF (genetic analysis) were eligible for this study. Acute exacerbation of pulmonary infection, intravenous use of tobramycin within 7 days prior to or during the study visits, impaired renal function (estimated glomerular filtration rate (eGFR) < 60 mL/min), use of loop diuretics and pregnancy or lactation were the exclusion criteria. According to their lung function, patients were categorized in subgroup 1, 2 or 3 corresponding to FEV1 (forced expiratory volume in the first second) predicted ≤59%, 60–79% or ≥80%, respectively. Each subgroup contained 6 patients.

The study was approved by the local ethics committee (METC Zuidwest Holland, The Netherlands) and the Central Committee on Research Involving Human Subjects (CCMO The Hague, The Netherlands) and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Full informed written consent was obtained from all patients.

2.2. Study design

In a randomized, open-label, crossover study lung deposition in 18 adult CF patients is evaluated following tobramycin inhalation using the I-neb nebulizer with TBM (Tidal Breathing Mode) and TIM (Target Inhalation Mode) breathing patterns. An off-label tobramycin solution and drug–device combination was used to assess the effect of breathing mode on aerosol lung deposition.

The study consisted of two visits for tobramycin inhalation, once with TBM and the other time with TIM, in random order and separated by a week washout. On both days patients received a physical examination, kidney function (eGFR) was established and spirometry (Jaeger Masterscreen PFT, CareFusion, Hoechberg, Germany) was performed according to the ATS/ERS guidelines [9]. Blood samples were collected for tobramycin analysis. Venous blood samples were taken in the hospital before and 15, 30 and 60 min after the start of each inhalation. Dried blood spots were collected by patients themselves at home 3, 4, 6 and 24 h after inhalation [10].

2.3. Inhalation procedure

Tobramycin was administered with the I-neb AAD system (Philips, Respironics, Chichester, United Kingdom) in combination with a white 1 mL medication chamber. This nebulizer combines Adaptive Aerosol Delivery (AAD) with Vibrating Mesh Technology (VMT). In AAD the nebulizer monitors and adapts to the individual breathing pattern and medication is only delivered during inhalation [6]. With VMT the liquid medication is moved through a perforated metal mesh (2 μm) in order to create particles of a similar size [6]. The nebulizer can deliver aerosols with two different breathing patterns: TBM and TIM. In TBM the patient inhales during spontaneous tidal breathing and aerosols are pulsed during the first 50–80% of this inhalation [11]. With TIM the inspiratory flow is limited to approximately 20 L/min by a built-in resistance in the mouthpiece, which guides the patient to perform a slow and deep inhalation. Aerosols are pulsed during the complete extended inhalation except for the last second, in order to ensure sufficient time for pulmonary deposition [11]. Patients were all I-neb naive users and were trained in each breathing pattern prior to dosing. No active compound was inhaled during these training sessions. Subsequently, patients nebulized 1 mL of an ~10% tobramycin (as sulfate) solution with both breathing modes. Nebulization time was recorded.

2.4. Tobramycin analysis

Tobramycin sulfate (Spruyt Hillen, IJsselstein, The Netherlands) was dissolved in water for injection. A fresh solution was prepared for each patient under aseptic conditions, which was used for both study visits. Previous studies have shown that a device dose of 100 mg is sufficient to measure serum concentrations and that a 10% tobramycin inhalation solution is well tolerated [12,13].

The exact tobramycin concentration of each solution was measured before inhalation. After inhalation, the I-neb device, mouthpiece, medication chamber and exhalation filter (added to the standard device) were rinsed with sodium chloride 0.9% and the residual amount of tobramycin in the rinsing solutions was also measured. The net inhaled dose was calculated for each patient at each study visit. Tobramycin was measured in all blood samples with high-performance liquid chromatography (HPLC)–tandem mass spectrometry (MS/MS) [14]. The lower limit of quantification (LLOQ) was 0.1 mg/L with a coefficient of variation of <2.2%. The MULTIGEN tobramycin

immunoassay on an ARCHITECT c-8000 platform (Abbott Diagnostics, Hoofddorp, The Netherlands) was used to measure the amount of tobramycin in the I-neb rinse and inhalation solution (LLOQ = 0.2 mg/L).

2.5. Pharmacokinetic analysis

Individual pharmacokinetic parameters of tobramycin inhalation were calculated and assimilated with patient tobramycin serum values using a computerized CF-based Bayesian two-compartment open population pharmacokinetic model with first order absorption and first order elimination from the central compartment (MW-Pharm version 3.60, Mediware, Groningen, The Netherlands). The following parameters were calculated: maximum serum level (C_{max}), trough serum level (C_{trough}), time to maximum serum level (T_{max}) and area under the concentration–time curve ($AUC_{0–24\ h}$).

2.5.1. Main outcome measure

Bioavailability of aerosolized tobramycin, i.e., the fraction of the inhaled dose available for absorption, can be used as surrogate parameter for lung deposition, since tobramycin is not effectively absorbed by the gastrointestinal tract [15–18]. Bioavailability (F) of TIM relative to TBM (F_{rel}) was calculated with the formula: $F_{rel} = (AUC_{0–24\ hTIM} / AUC_{0–24\ hTBM}) \times (Dose_{TBM} / Dose_{TIM})$ in which the Dose represents the net inhaled dose, with the assumption of equal clearance on both inhalation days.

2.6. Statistical analysis

Statistical analysis was performed with SPSS version 17.0 (PASW Statistics, IBM Corporation, Armonk, USA). A mixed linear model with subgroup and study visit as fixed factors, gender and age as covariates and patient as random factor was used to estimate the effect of the breathing mode on pharmacokinetic parameters and nebulization time. In this model data were first evaluated for the absence of a possible order effect (breathing mode * study visit interaction). Paired t-tests were used to compare differences in eGFR, FEV1% predicted values and net inhaled dosages. The one-sample t-test was used to compare mean F_{rel} to the test value of 1. One-way ANOVA was used to test for differences between subgroups. P-values below 0.05 were considered to be statistically significant. The guideline on the investigation of bioequivalence [19] from the committee for medicinal products for human use (CHMP) was used to provide a statement about the clinical relevance of the differences between the breathing modes. In accordance with this guideline C_{max} and $AUC_{0–24\ h}$ were compared using a general linear model in order to assess equivalence.

3. Results

3.1. Study population

Eighteen CF patients (10 males), aged 19–57 years (mean 33.9 years), were included in the study. Overall, there were no significant differences in eGFR, FEV1% predicted and net inhaled dose between both study visits (Table 1). Only subgroup 2 showed a significant difference in FEV1% predicted between the two study days.

3.2. Pharmacokinetics

The individual calculated pharmacokinetic parameters are summarized in Table 2. Mean C_{max} and $AUC_{0–24\ h}$ were significantly increased for TIM compared to TBM for the entire study population ($P < 0.001$). TIM inhalation also resulted in a higher mean C_{max} and $AUC_{0–24\ h}$ in each subgroup, though these differences were not always significant. Differences in C_{max} and $AUC_{0–24\ h}$ between the three subgroups were not statistically significant and no significant interaction effects between study visit (day 1 or 2) and breathing mode or between subgroup (disease severity) and breathing mode for C_{max} and $AUC_{0–24\ h}$ were found.

F_{rel} was 1 or higher for all patients and the mean F_{rel} of 1.53 was significantly higher than the value of 1 ($P < 0.001$, 95% CI = 1.32–1.73). Fig. 1 shows the relative increase in tobramycin bioavailability for TIM compared to TBM inhalation. In addition, mean F_{rel} was also significantly higher than 1 in each of the three subgroups separately (Table 2). Differences in F_{rel} between the three subgroups were not statistically significant.

Table 3 shows the clinical relevance of differences in C_{max} and $AUC_{0–24\ h}$ when comparing TIM to TBM inhalation. All noted differences in these parameters were considered to be clinically relevant between the two breathing modes.

3.3. Nebulization time

The mean nebulization time was significantly shorter with TIM (7.63 ± 1.66 min) compared to TBM (16.34 ± 4.09 min)

Table 1
Patient characteristics and inhaled dose.

Study population n = 18 Subgroup n = 6	TIM	TBM	P-value[a]
eGFR (mL/min) study population	114.92 ± 23.74	119.20 ± 30.45	NS
Subgroup 1	112.00 ± 26.65	117.60 ± 34.62	NS
Subgroup 2	95.50 ± 34.65	106.83 ± 31.47	NS
Subgroup 3	123.83 ± 17.03	139.75 ± 14.32	NS
FEV1% predicted study population	67.44 ± 20.48	68.83 ± 21.37	NS
Subgroup 1	46.67 ± 13.19	46.17 ± 12.12	NS
Subgroup 2	65.17 ± 5.81	67.67 ± 7.55	0.026
Subgroup 3	90.50 ± 7.50	92.67 ± 7.03	NS
Net inhaled dose (mg) study population	71.77 ± 16.45	71.76 ± 13.15	NS
Subgroup 1	75.11 ± 15.21	73.29 ± 12.61	NS
Subgroup 2	58.48 ± 11.62	65.82 ± 16.00	NS
Subgroup 3	81.73 ± 14.44	76.18 ± 10.22	NS

Data are presented as mean ± sd. TIM = Target Inhalation Mode; TBM = Tidal Breathing Mode; eGFR = estimated glomerular filtration rate based on the Modification of Diet in Renal Disease (MDRD) equation; FEV1 = forced expiratory volume in the first second; Subgroup 1 ≤ 59, 2 = 60–79, 3 ≥ 80 FEV1% predicted; NS = not statistically significant.

[a] P-values are calculated using paired t-tests.

Table 2
Pharmacokinetic parameters.

Study population n = 18 Subgroup n = 6	TIM	TBM	P-value[a]
C_{max} (mg/L) study population	1.22 ± 0.46	0.82 ± 0.39	<0.001
Subgroup 1	1.09 ± 0.63	0.63 ± 0.28	0.046
Subgroup 2	1.10 ± 0.42	0.73 ± 0.50	0.083
Subgroup 3	1.48 ± 0.19	1.10 ± 0.22	0.011
AUC_{0-24} (h·mg/L) study population	8.45 ± 2.85	5.79 ± 2.21	<0.001
Subgroup 1	7.88 ± 4.43	4.64 ± 1.89	0.057
Subgroup 2	7.80 ± 2.05	5.48 ± 2.85	0.054
Subgroup 3	9.68 ± 1.01	7.24 ± 0.88	0.004
C_{trough} (mg/L) study population	0.22 ± 0.073	0.15 ± 0.052	<0.001
Subgroup 1	0.21 ± 0.12	0.13 ± 0.048	0.063
Subgroup 2	0.21 ± 0.045	0.14 ± 0.065	0.024
Subgroup 3	0.25 ± 0.029	0.19 ± 0.018	0.004
T_{max} (min) study population	87.83 ± 12.54	91.00 ± 16.44	0.406
Subgroup 1	89.33 ± 13.97	86.67 ± 7.69	0.711
Subgroup 2	92.67 ± 13.56	101.00 ± 20.96	0.432
Subgroup 3	81.50 ± 8.78	85.33 ± 15.46	0.674
F_{rel} study population	1.53 ± 0.41		<0.001
Subgroup 1	1.58 ± 0.38		0.014
Subgroup 2	1.74 ± 0.52		0.017
Subgroup 3	1.26 ± 0.13		0.004

Data are presented as mean ± sd. Pharmacokinetic parameters following tobramycin inhalation using the I-neb nebulizer (see Table 1 for mean net inhaled dosages). TIM = Target Inhalation Mode; TBM = Tidal Breathing Mode; C_{max} = maximum serum level; C_{trough} = trough serum level, 12 h after dose; T_{max} = time to maximum serum level; $AUC_{0-24\ h}$ = area under the concentration–time curve from 0 to 24 h; F_{rel} = bioavailability of TIM relative to TBM, calculated with ($AUC_{0-24\ hTIM}$ / $AUC_{0-24\ hTBM}$) × ($Dose_{TBM}$ / $Dose_{TIM}$); Subgroup 1 ≤ 59, 2 = 60–79, 3 ≥ 80 FEV1% predicted; FEV1 = forced expiratory volume in the first second.

[a] P-values for C_{max}, C_{trough}, T_{max}, and $AUC_{0-24\ h}$ are derived from a linear mixed model with study visit (day 1 or 2) and subgroup as fixed factors, gender and age as covariates and patient as random factor. P-values for F_{rel} are calculated with the one-sample t-test with a test value of 1.

Table 3
Clinical relevance.

Study population n = 18 Subgroup n = 6	Geometric mean		Ratio geometric mean (90% CI)	Clinically relevant?[a]
	TIM	TBM	TIM vs. TBM	Difference TIM to TBM
C_{max} (mg/L) study population	1.12	0.74	1.52 (1.33–1.73)	Yes
Subgroup 1	0.94	0.58	1.60 (1.27–2.02)	Yes
Subgroup 2	1.01	0.63	1.61 (1.09–2.37)	Yes
Subgroup 3	1.46	1.08	1.36 (1.16–1.59)	Yes
$AUC_{0-24\ h}$ (h·mg/L) study population	7.88	5.38	1.47 (1.31–1.64)	Yes
Subgroup 1	6.75	4.33	1.56 (1.25–1.95)	Yes
Subgroup 2	7.52	5.00	1.50 (1.08–2.09)	Yes
Subgroup 3	9.64	7.19	1.34 (1.21–1.49)	Yes

Clinical relevance of differences in C_{max} and $AUC_{0-24\ h}$ when comparing TIM to TBM breathing pattern. TIM = Target Inhalation Mode; TBM = Tidal Breathing Mode; C_{max} = maximum serum level; $AUC_{0-24\ h}$ = area under the time–concentration curve from 0 to 24 h; Subgroup 1 ≤ 59, 2 = 60–79, 3 ≥ 80 FEV1% predicted; FEV1 = forced expiratory volume in the first second; CI = confidence interval.

[a] The difference is considered to be clinically relevant when the 90% CI for the geometric mean ratio of a parameter does not fall completely within the acceptance interval of 0.80–1.25 and bioequivalence cannot be concluded (derived from the CHMP guideline on the investigation of bioequivalence [19]).

inhalation (P < 0.001) (Fig. 2a). Significant differences were also noted for all three subgroups (Fig. 2b). These differences were independent from disease severity and it did not matter whether a patient used the TIM breathing pattern during his first or second study visit. Although no significant subgroup effect was found, nebulization time tends to shorten with better lung function for both TIM and TBM inhalation (Fig. 2b).

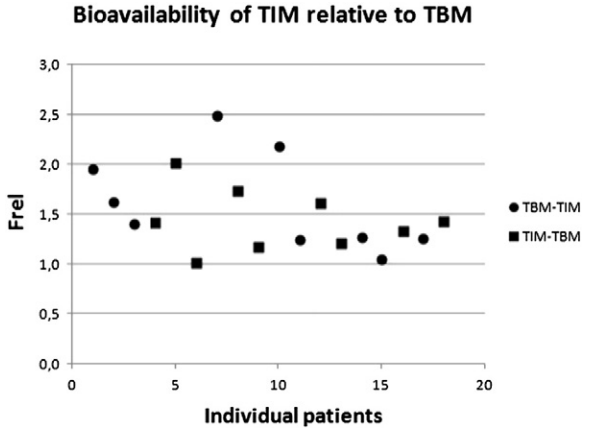

Fig. 1. Relative increase in tobramycin bioavailability as surrogate parameter for lung deposition when using TIM compared to TBM breathing pattern, represented by the relative bioavailability (F_{rel}). Every dot or square represents one patient; dots when randomized to inhale with TBM during study visit 1 and squares when randomized to start with TIM inhalation. F_{rel} is the bioavailability of TIM relative to TBM, calculated with ($AUC_{0-24\ hTIM}$ / $AUC_{0-24\ hTBM}$) × ($Dose_{TBM}$ / $Dose_{TIM}$). TIM = Target Inhalation Mode; TBM = Tidal Breathing Mode; $AUC_{0-24\ h}$ = area under the concentration–time curve from 0 to 24 h.

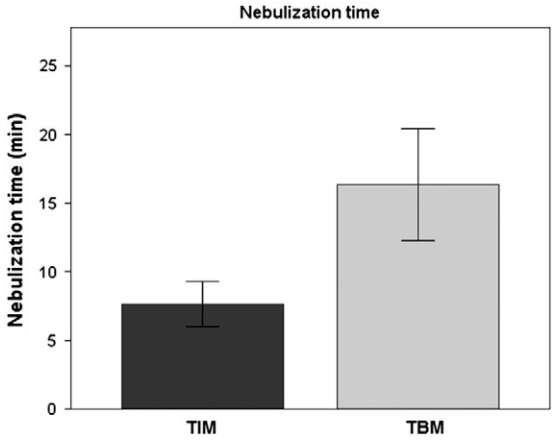

Fig. 2a. Mean nebulization time for TIM and TBM breathing patterns. The error bars represent the standard deviations. TIM = Target Inhalation Mode; TBM = Tidal Breathing Mode.

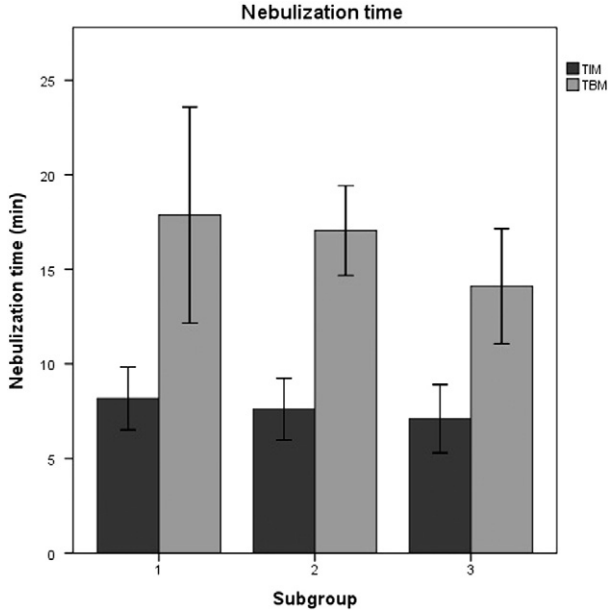

Fig. 2b. Mean nebulization time for TIM and TBM per subgroup: 1 ≤ 59, 2 = 60–79, 3 ≥ 80 FEV1% predicted. The error bars represent the standard deviations. Correlation coefficients as a measure of the strength and direction of a linear relationship between nebulization time and subgroup (lung function) are R = 0.999 and R = 0.904 for TIM and TBM breathing patterns, respectively. TIM = Target Inhalation Mode; TBM = Tidal Breathing Mode; FEV1 = forced expiratory volume in the first second.

4. Discussion

This study demonstrated that slow and deep inhalation (TIM) of aerosolized tobramycin with the I-neb nebulizer resulted in 53% higher total lung deposition compared to normal tidal breathing (TBM) in patients with CF based on pharmacokinetic data. We have also shown that TIM inhalation reduced treatment time by half. Finally, these results were found to be independent from disease severity, as reflected by the patients' lung function.

The results of this study are in good agreement with recent trials investigating other novel controlled-inhalation techniques, in which slow and deep breathing shows to be advantageous over spontaneous breathing [20–23].

Although pharmacokinetic data has been used before and is considered to be a simple, rapid and cheap method to compare lung deposition between inhalation devices/techniques [8,15,24,25], there are some drawbacks to this method. Most important, pharmacokinetics only reflect total lung deposition and relationships between serum levels and regional lung exposure are not established yet [26]. However, we think that given the poor oral absorption and low epithelial membrane crossing of tobramycin [15], combined with the knowledge that a slow deep breathing pattern is beneficial for peripheral deposition [5], higher tobramycin serum levels are indicative for higher deposition in the peripheral airways, where conditions for absorption are better compared to the central lung. Hence, the higher C_{max} and $AUC_{0–24\ h}$ achieved with TIM inhalation in our study indicates higher peripheral deposition. Although no direct relationships between drug deposition site and clinical outcomes have been established in CF yet, it is expected that peripheral targeting will result in a higher *Pseudomonas* drug exposure leading to a better anti-pseudomonal effect [2]. A recent study in children with CF inhaling dornase alfa showed greater improvement in lung function when peripheral deposition was targeted compared to central airway targeting [27]. Studies with asthmatic patients also showed that regional deposition is a better predictor of clinical outcome than total lung deposition [28,29]. Further investigations are necessary exploring these relationships in CF.

C_{max}, T_{max} and AUC are most frequently used as indirect pharmacokinetic parameters to evaluate pulmonary drug deposition. When comparing breathing modes intra-individual, AUC is probably the best descriptor for deposition, since the difference in nebulization time between slow deep and normal tidal breathing can influence C_{max} and T_{max}. Although the $AUC_{0–24\ h}$ was significantly increased for TIM compared to TBM for the entire study population and for patients included in subgroup 3, differences in $AUC_{0–24\ h}$ between the breathing modes in subgroups 1 and 2 did not reach significance (Table 2). A small number of patients per subgroup and a relative large variation in subgroups 1 and 2 could have contributed to this result. In addition, the wide range of net inhaled tobramycin dosages presumably played a role (Table 1). However, when looking at the main outcome measure F_{rel}, calculated from AUCs corrected for the inhaled dosages, it was found that TIM inhalation resulted in significant higher bioavailability, i.e., higher lung deposition, for both the entire study population as for all subgroups.

We considered all differences in C_{max} and $AUC_{0–24\ h}$ clinically relevant based on the accepted methods of bioequivalence assessment [19] (Table 3). This implies that slow and deep breathing results in a clinically significant higher pulmonary drug deposition. However, whether this breathing mode truly leads to clinically better treatment effects should be investigated in trials with clear efficacy outcomes.

We did not find a significant difference in T_{max} between the two breathing modes. Because nebulization time with TIM was shorter and no significant differences in dosages between the study visits existed, we also expected C_{max} to be reached earlier when comparing to TBM inhalation. An explanation may be that within the timeframe of this nebulization pulmonary absorption is mainly determined by rate limited absorption kinetics [12,13].

Because of the cross-over setting in this study we expected the intra-individual variability to be low. Indeed, of all parameters only a significant difference in FEV1% between breathing modes was found in patients included in subgroup 2 (Table 1). Though, the largest absolute difference in FEV1% predicted for a patient in this subgroup was 7%, which was not considered to be clinically relevant. The results of this study were based on a small study population, which is a limitation. However, a sample size of 6 to 18 patients is quite common in pharmacokinetic studies [8,12,13,21,30–32]. Inter-patient variability in lung deposition can be large in patients with CF [8], which makes it difficult to extrapolate results from small trials to other patients. Heterogeneity in disease severity may contribute to this variability and patients were therefore categorized in three subgroups according to their lung function. However, no significant interaction effects between subgroup and breathing mode were found in our study.

Hence, the observed differences in pharmacokinetic parameters could not be explained by the patients' disease severity.

This study demonstrated a 53% increase in bioavailability by inhaling slowly. In clinical trials, serum levels are often used as a safety measure and, therefore, recommending slow deep tobramycin inhalation may change the safety margin. C_{max} and C_{trough} stayed well below toxic limits in our study with both breathing modes. It is important to emphasize that an off-label device and tobramycin solution/dose were used solely to demonstrate the potential for slow deep inhalation to improve lung deposition in CF. Clinical trials are necessary and planned to demonstrate the efficacy and safety of this approach. However, since the recommended dose of the licensed tobramycin solutions (60 to 75 mg) is lower than the dose used in this study (100 mg), toxic serum levels are not expected in daily clinical practice.

A more than two times shorter nebulization time was attained with slow and deep inhalation, which is in good agreement with data from other clinical trials [7,33,34]. Since treatment burden is considered to be high in CF patients, a shorter nebulization time can contribute to a higher treatment adherence, better therapeutic effect and improvement of quality of life [33,34]. The clinical experience of TIM inhalation in CF has been evaluated in several studies [33–35]. These studies indicate that TIM is an acceptable and easy to use breathing mode for patients with CF at all ages.

Tobramycin can also be administered as inhalation powder by the TOBI® Podhaler (Novartis AG, Basel, Switzerland). Comparative studies with the conventional Pari LC Plus jet nebulizer (PARI GmbH, Starnberg, Germany) have shown comparable lung deposition between the powder and solution, though, four times faster treatment times were attained with the powder inhalation [25,36]. The average treatment time for powder administration is approximately 4–6 min [37], which is also faster than or similar to tobramycin TIM inhalation. However, not all CF patients tolerate the powder formulation, since it is associated with more local adverse events [36]. Moreover, no differences in peripheral versus central deposition between the two formulations were demonstrated [38]. Hence, peripheral targeting is not improved by the use of a powder inhaler.

In conclusion, this pharmacokinetic study showed higher tobramycin deposition following slow deep inhalation compared to tidal breathing in CF patients, regardless of the disease severity of the patient. Presumably higher peripheral deposition is achieved with a slow deep breathing mode, which may yield better clinical results. Slow deep inhalation also shortened treatment time considerably. This suggests that a slow and deep breathing mode would be beneficial for all CF patients needing antibiotic inhalation therapy. Clinical trials investigating targeted aerosol deposition in direct relationship to efficacy and long-term safety of tobramycin TIM inhalation in a large cohort of CF patients are required to support these conclusions.

Conflict of interest statements

All authors report a research grant from the cystic fibrosis foundations from Luxembourg (Association Luxembourgeoise de Lutte contre la Mucoviscidose; ALLM) and The Netherlands (Nederlandse Cystic Fibrosis Stichting; NCFS), during the conduct of the study.

Role of the funding source

The study was supported by a research grant from the cystic fibrosis foundations from Luxembourg (ALLM) and The Netherlands (NCFS). These foundations were not involved in the study design, collection, analysis and interpretation of data and/or writing of the manuscript.

Contribution of authors

A.J. van Velzen, PharmD, is the primary investigator and corresponding author of this study. She made substantial contributions to the acquisition, analysis and interpretation of the data, has drafted and revised the submitted manuscript critically, has provided final approval of the version to be published and is taking responsibility for the accuracy and integrity of any part of the work.

J.W.F. Uges, PharmD, made substantial contributions to the conception and design of the work, the acquisition, analysis and interpretation of data, has revised the submitted manuscript critically, has provided final approval of the version to be published and is taking responsibility for the accuracy and integrity of any part of the work.

P. Shahbabai, MSc, made substantial contributions to the acquisition and analysis of the data, has revised the submitted manuscript critically, has provided final approval of the version to be published and is taking responsibility for the accuracy and integrity of any part of the work.

P.P.H. Le Brun, PharmD, PhD, made substantial contributions to the conception and design of the work, has revised the submitted manuscript critically, has provided final approval of the version to be published and is taking responsibility for the accuracy and integrity of any part of the work.

Prof. D.J. Touw, PharmD, PhD, made substantial contributions to the analysis and interpretation of the data, has revised the submitted manuscript critically, has provided final approval of the version to be published and is taking responsibility for the accuracy and integrity of any part of the work.

H.G.M. Heijerman, MD, PhD, made substantial contributions to the conception and design of the work, has revised the submitted manuscript critically, has provided final approval of the version to be published and is taking responsibility for the accuracy and integrity of any part of the work.

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